Trend Watch

Treatment of Fibromyalgia

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ABSTRACT

In this article, we investigate the range of treatments prescribed for fibromyalgia. The data suggest that the majority of those treated, 82 percent, receive only one pharmaceutical. An additional 12 percent of patients were prescribed two products and six percent received three products. Pregabalin (Lyrica®) monotherapy was the most commonly prescribed regimen (21% of patients) followed by duloxetine (Cymbalta®) monotherapy (20%). From a therapeutic class perspective, fibromyalgia patients received antidepressants (46%), antiepileptics (35%), pain therapies (25%), muscle relaxants (8%), and sleep agents (2%). An expert commentary is included.

KEY WORDS

fibromyalgia, pregabalin, duloxetine, milnacipran, gabapentin, pharmacology

INTRODUCTION

In January 2009, milnacipran (Savella®) was approved by the United States Food and Drug Administration (FDA) as a new treatment for fibromyalgia (FM). Since that time, Jazz Pharmaceuticals filed an new drug application (NDA) for sodium oxybate (Xyrem®) in February, 2010. Other approved treatments include duloxetine (Cymbalta®) and pregabalin (Lyrica®). To better understand current practice patterns, in this article, we investigate and discuss the range of treatments prescribed to patients with fibromyalgia.

METHODS

We obtained data on product treatment regimens from SDI Health's Prescription Drug and Diagnosis Audit (PDDA) database from February 2009 to January 2010 for patients with fibromyalgia as defined by SDI Health's diagnosis code 729140. PDDA captures data on disease states and associated therapies from 3,200 office-based physicians representing 30 specialties across the United States. Information from physicians on reasons for drug use is translated by SDI Health analysts into 3-digit, 4-digit, and 5-digit ICD-9 diagnosis codes, as well as a 6-digit code developed by SDI Health for conditions, such as FM, where the ICD-9 coding is nonspecific.

RESULTS

According to practice data from SDI Health, approximately 91 percent of patients presenting with FM are women. Figure 1 displays the number of products typically prescribed to treat FM. As seen in Figure 1, 82 percent of patients are prescribed only one agent, 12 percent are prescribed two

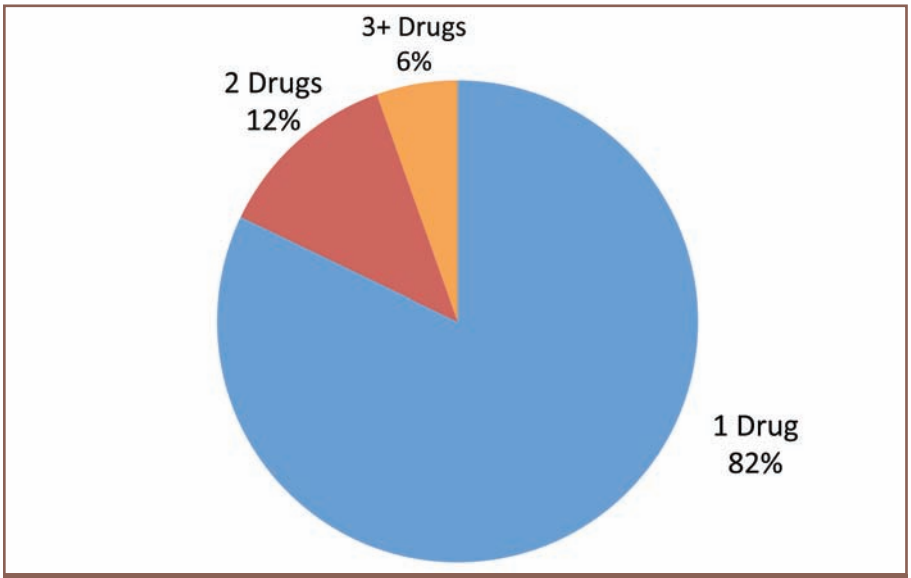

FIGURE 1. Number of products used to treat fibromyalgia
SOURCE: SDI Health PDDA, Diagnosis 729140, February 2009 to January 2010

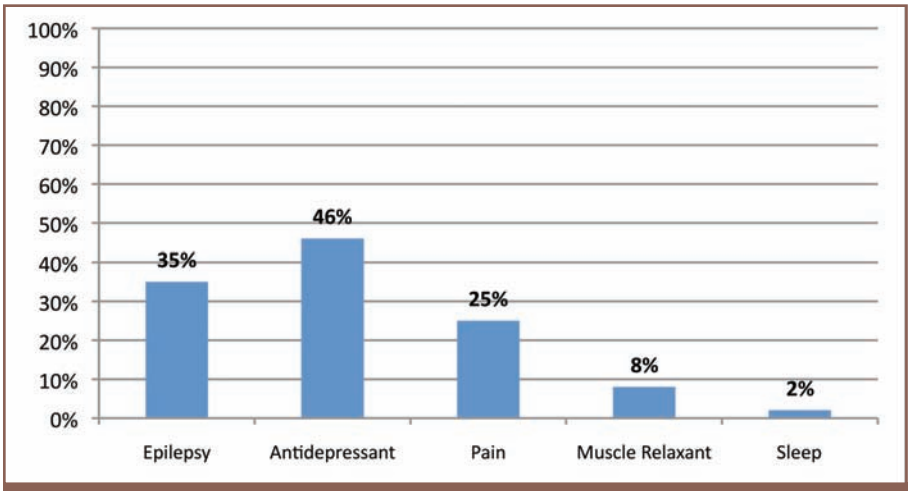

FIGURE 2. Classes prescribed to treat fibromyalgia
SOURCE: SDI Health PDDA, Diagonsis 729140, February 2009 to January 2010

products, and six percent are prescribed three or more products.

Pregabalin monotherapy is the treatment most commonly prescribed (21% of patients); duloxetine monotherapy is the second most popular regimen accounting for an additional 20 percent of uses. Since approval in January 2009, milnacipran monotherapy has emerged as a common treatment with 10 percent of uses.

From a therapeutic class perspective, the agents most commonly prescribed to patients with FM are antidepressants (46%)—primarily duloxetine, milnacipran, or some tricyclic antidepressants. Antiepileptics (35%, mainly pregabalin) are the second most common regimen. Other classes include pain therapies (25%), muscle relaxants (8%), and sleep agents (2%) (Figure 2).

EXPERT COMMENTARY

by Roland M. Staud, MD

FM is a chronic pain disorder characterized by widespread pain, stiffness, insomnia, fatigue, and distress. Like many other chronic pain syndromes, the pathophysiology of FM comprises abnormal sensory processing in the peripheral and central nervous system as well as dysfunction of the stress response systems, including the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal axis (HPA).[1–3]

Several randomized, controlled trials (RCT) have shown moderate effectiveness of pharmacological therapies for FM pain.[4] Evidence from these trials suggests that pharmacological therapy cannot only improve pain but can also improve fatigue, function, and well-being of patients with FM. The alpha2-delta agonist pregabalin, as well as duloxetine and milnacipran, two highly selective serotonin-norepinephrine-reuptake inhibitors (SNRI), have been approved by the FDA for the treatment of FM symptoms. In general, about half of all patients treated with any one of these medications seem to experience a 30-percent reduction of symptoms, suggesting that many patients with FM will require additional therapies. Thus it is interesting that, according to the Trend Watch data in this article, most FM patients (82%) treated by a variety of medical specialists had only one drug prescribed for treatment of their symptoms. From this evidence, one may surmise that FM patients in general clinical practice either required less pain

relief, i.e. had low levels of pain to begin with, or that nonpharmacological treatments, including exercise, cognitive behavioral therapies, and self-management strategies contributed to satisfactory treatment outcomes. On the other hand, one could also conclude that many FM patients have been left undertreated.

The most frequently prescribed pharmacological treatments of FM patients in this Trend Watch data (46%) included antidepressants. These medications exert their effects at the serotonin (5-HT) and norepinephrine (NE) transporters of the presynaptic terminals of neurons. Whereas most tricyclic antidepressants (TCA) provide balanced reuptake inhibition of 5-HT and NE, newer dual uptake inhibitors, including 5-HT-NE reuptake inhibitors (SNRIs) and NE-5-HT reuptake inhibitors (NSRIs), are considered to be more effective for treatment of FM symptoms than pure serotonergic or noradrenergic agents. These latter drugs are similar to TCAs in their ability to inhibit the reuptake of both 5-HT and NE but, unlike TCAs, they do not possess significant affinity to other receptor systems. This selectivity results in diminished side effects and enhanced tolerability. Available trial data for venlafaxine, the first SNRI on the market, support its use in the management of neuropathic pain and FM.[5] Several additional SNRIs and NSRIs, including duloxetine and milnacipran, have been studied in randomized controlled trials (RCT) of patients with FM (see below). Although many chronic pain syndromes, including FM, show high comorbidity with depression, several trials showed that the analgesic efficacy of antidepressants was independent of their effects on mood.[6] Overall, a recent meta-analysis of 18 RCTs confirmed that antidepressants can improve FM pain, depression, fatigue, sleep disturbances, and health-related quality of life.[7]

Antiepileptic drugs are widely used in the treatment of neuropathic pain conditions, including postherpetic neuralgia and painful diabetic neuropathy.[8] Among these, gabepentin (Neurontin®) and pregabalin (Lyrica®) play an important role for the treatment of neuropathic pain. Pregabalin, whose precursor is gabapentin, has analgesic, anxiolytic, and antiepileptic effects. Like gabapentin, pregabalin binds to the $\alpha 2\delta$ subunit of voltage-gated calcium channels in the central nervous system without affecting γ-aminobutyric acid (GABA) receptors. Its activity is limited to neurons and it does not affect vascular calcium channels. However, the exact mechanism of action of pregabalin on FM pain is unknown. Reduction of calcium influx into neurons may reduce the release of substance P, glutamate, and NE, which is thought to mediate pregabalin's analgesic and anxiolytic actions.

Several treatment strategies for FM symptoms appear useful at this time: A) reduction of peripheral pain generators, particularly from muscles, B) improvement or prevention of central sensitization, C) normalization of sleep abnormalities, and D) treatment of negative affect, particularly depression. The first strategy is most likely relevant for acute FM pain exacerbations and includes physical therapy, muscle relaxants, muscle injections, and analgesics. Limited evidence appears to indicate that central sensitization can be successfully ameliorated by antidepressants and antiseizure medications, but also by cognitive behavioral therapy and sleep improvement. Sleep dysfunction can be normalized by stress reduction, aerobic exercise, and GABA agonists. The pharmacological and behavioral treatment of secondary pain affect (anxiety, anger, depression, and fear) is equally important and may currently be one of the most powerful interventions for FM pain. Although future therapies with any combination of the above mentioned interventions will likely be beneficial for patients with FM, only head-to-head comparison trials will provide evidence for the superiority of one treatment over another. However, as with many other chronic syndromes, risk stratification and prevention will be of greatest importance and benefit for FM.

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